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> d his


     (FILE 'USPAT' ENTERED AT 16:20:03 ON 18 JAN 1999)
L1           236 S MAGE
L2          2713 S CD4
L3            61 S L1 AND L2
L4          2387 S CLASS II
L5            26 S L3 AND L4
L6             0 S 1-26 CIT
L7            26 S L5
                 E BOON T/IN
                 E BOONS E2
                 E BOON T/IN
L8            40 S E2
L9            30 S L1 AND L8
L10            1 S L9 AND L2
L11           30 S L9
L12            1 S L9 AND L4
L13          565 S L2 AND L4
L14           26 S L13 AND L1
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(FILE 'HOME' ENTERED AT 16:52:04 ON 18 JAN 1999)

FILE 'MEDLINE' ENTERED AT 16:52:10 ON 18 JAN 1999

L1	35497	S	CD4
L2	31209	S	CLASS II
L3	3424	S	L1 AND L2
L4	265	S	MAGE
L5	1	S	L3 AND L4

TI Human **CD4**+ T cells specifically recognize a shared melanoma-associated antigen encoded by the **tyrosinase** gene.

AU Topalian S L; Rivoltini L; Mancini M; Markus N R; Robbins P F; Kawakami Y;
Rosenberg S A

CS Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892..

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Sep 27) 91 (20) 9461-5.
Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199501

AB Although commonly expressed human melanoma-associated antigens recognized by CD8+ cytolytic T cells have been described, little is known about **CD4**+ T-cell recognition of melanoma-associated antigens. Epstein-Barr virus-transformed B cells were used to present antigens derived from whole cell lysates of autologous and allogeneic melanomas for recognition by melanoma-specific **CD4**+ T-cell lines and clones cultured from tumor-infiltrating lymphocytes. HLA-DR-restricted antigens were detected in the lysates on the basis of specific release of cytokines from the responding T cells. Antigen sharing was demonstrated in the majority of melanomas tested, as well as in cultured normal melanocytes, but not in other normal tissues or nonmelanoma tumors. T-cell clones manifested a single recognition pattern, suggesting the presence of an immunodominant epitope. This epitope was identified as a product of the **tyrosinase** gene, which has also been shown to encode class I-restricted epitopes recognized by CD8+ T cells from melanoma patients. Identification of commonly expressed tumor-associated protein molecules containing epitopes presented by both class I and class II major histocompatibility molecules may provide optimal reagents for cancer immuni

L2 ANSWER 26 OF 27 MEDLINE
AN 94280772 MEDLINE
DN 94280772
TI Tumor antigens recognized by T lymphocytes.
AU Boon T; Cerottini J C; Van den Eynde B; van der Bruggen P; Van Pel A
CS Ludwig Institute for Cancer Research, Brussels, Belgium.
SO ANNUAL REVIEW OF IMMUNOLOGY, (1994) 12 337-65. Ref: 176
Journal code: ALO. ISSN: 0732-0582.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199409
AB Transplantation experiments have demonstrated that most mouse tumors express antigens that can constitute targets for rejection responses mediated by syngeneic T lymphocytes. For human tumors, autologous cultures mixing tumor cells and blood lymphocytes or tumor-infiltrating lymphocytes have produced CD8+ and **CD4**+ cytolytic T cell (CTL) clones that recognize tumor cells specifically. Attempts to identify the target antigens by biochemical fractionation of tumor cells up to now have failed, with the important exception of the identification of underglycosylated mucins present on breast and pancreatic carcinomas. Gene transfection approaches have proved more successful. A gene family named MAGE codes for antigens recognized by autologous CTL on a melanoma tumor. These genes are not expressed in normal tissues except for testis. They are expressed in many tumors of several histological types. Differentiation antigens coded by genes such as **tyrosinase** are also recognized on human melanoma by autologous CTL. The identification of human tumor rejection antigens opens new possibilities for systematic approaches to the specific immune therapy of cancer.

L6 ANSWER 3 OF 4 MEDLINE
AN 96213700 MEDLINE
DN 96213700
TI New treatment options for patients with melanoma: review of melanoma-derived T-cell epitope-based peptide vaccines.
AU Maeurer M J; Storkus W J; Kirkwood J M; Lotze M T
CS Department of Biochemistry, University of Pittsburgh Cancer Insitute, PA, USA.
SO MELANOMA RESEARCH, (1996 Feb) 6 (1) 11-24. Ref: 102
Journal code: BJR. ISSN: 0960-8931.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199609
AB Human melanoma represents the principal cause of death in patients with skin cancer in the United States and Europe. Tumour infiltrating lymphocytes recognizing melanoma have been used to identify the tumour antigens recognized by T-cells in the context of **MHC** class I or class **II** molecules. Such antigens include MAGE-1, MAGE-3, MART-1/Melan-A, gp100, **tyrosinase**, the **tyrosinase** -related antigen gp75, the antigen gp15 and the mutated CDK4 and beta-catenin gene-products. The identification of these T-cell epitopes provides us with novel reagents for the development of state-of-the-art treatments and for the (immuno-)monitoring of patients with melanoma. In order for treatments, including peptide-based vaccines, to be successful, several conceptual criteria must be met: (1) The patient's tumour must present the relevant epitope(s) integrated into the vaccine, (2) the tumour should express the appropriate restricting major histocompatibility complex (MHC) molecule(s) required for patient cytotoxic T lymphocyte (**CTL**) reactivity, and (3) the patient's T-cell repertoire should be able to react productively against the melanoma antigens present in the vaccine. Clinical trials implementing peptide-based vaccines or whole protein therapies have been initiated in the United States and Europe. We suggest that such treatments should include the careful monitoring of anti-tumour T-cell responses. This should include examination of melanoma antigen and MHC class I allele expression in the individual patient's tumour, assessment of the status of the peptide transporter molecules TAP1/TAP2 and evaluation of T-cell mediated immune responses reactive against peptides and autologous melanoma. Evaluation of clinical parameters (such as disease-free survival) in conjunction with an examination of immunological parameters may facilitate our understanding of the immune responses against T-cell antigens that are shared among melanoma and normal melanocytes, and may ultimately help to identify the most effective immunotherapy for patients with melanoma.

L6 ANSWER 4 OF 4 MEDLINE
AN 96195205 MEDLINE
DN 96195205
TI An HLA-A2-restricted **tyrosinase** antigen on melanoma cells results from posttranslational modification and suggests a novel pathway for processing of membrane proteins.
AU Skipper J C; Hendrickson R C; Gulden P H; Brichard V; Van Pel A; Chen Y; Shabanowitz J; Wolfel T; Slingluff C L Jr; Boon T; Hunt D F; Engelhard V H
CS Department of Microbiology, University of Virginia, Charlottesville 22908,

USA.
NC AI-20963 (NIAID)
CA-57653 (NCI)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Feb 1) 183 (2) 527-34.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199608
AB T lymphocytes recognize antigens consisting of peptides presented by class I and **II** major histocompatibility complex (**MHC**) molecules. The peptides identified so far have been predictable from the amino acid sequences of proteins. We have identified the natural peptide target of a **CTL** clone that recognizes the **tyrosinase** gene product on melanoma cells. The peptide results from posttranslational conversion of asparagine to aspartic acid. This change is of central importance for peptide recognition by melanoma-specific T cells, but has no impact on peptide binding to the MHC molecule. This posttranslational modification has not been previously described for any MHC-associated peptide and represents the first demonstration of posttranslational modification of a naturally processed class I-associated peptide. This observation is relevant to the identification and prediction of potential peptide antigens. The most likely mechanism for production of this peptide leads to the suggestion that antigenic peptides can be derived from proteins that are translated into the endoplasmic reticulum.

No date.

L2 ANSWER 22 OF 27 MEDLINE
AN 96235006 MEDLINE
DN 96235006
TI Melanoma-specific **CD4**+ T cells recognize nonmutated HLA-DR-restricted **tyrosinase** epitopes.
AU Topalian S L; Gonzales M I; Parkhurst M; Li Y F; Southwood S; Sette A; Rosenberg S A; Robbins P F
CS Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 May 1) 183 (5) 1965-71.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199609
AB **Tyrosinase** was the first melanoma-associated antigen shown to be recognized by **CD4**+ T cells. In this study, we have identified two HLA-DRB1*0401-restricted peptides recognized by these T cells: Ty 56-70 and Ty 448-462. As with many of the MHC class I-restricted melanoma epitopes, both are nonmutated self peptides that have intermediate and weak MHC binding affinities, respectively. Mutated and truncated versions of these peptides were used to define their MHC binding anchor residues. Anchor residues were then modified to derive peptides with increased MHC binding affinities and T cell stimulatory properties. Ty 56-70 and Ty 448-462 enhance the list of immunogenic HLA-A2-, A24-, and B44-restricted **tyrosinase** peptides already described. Thus, **tyrosinase** provides a model for anti-melanoma vaccines in which a single molecule can generate multivalent immunization incorporating both **CD4**+ and CD8+ T

TI Isolation of **tyrosinase**-specific CD8+ and **CD4**+ T cell clones from the peripheral blood of melanoma patients following in vitro stimulation with recombinant vaccinia virus.

AU Yee C; Gilbert M J; Riddell S R; Brichard V G; Fefer A; Thompson J A; Boon T; Greenberg P D

CS Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98104, USA.

SO JOURNAL OF IMMUNOLOGY, (1996 Nov 1) 157 (9) 4079-86.
Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199702

EW 19970204

AB The identification of Ags expressed by tumor cells and recognized by autologous T cells has led to the prospect of treating cancer by adoptive transfer of tumor-reactive T cells selected for Ag specificity. **Tyrosinase** is an Ag expressed by normal melanocytes as well as melanoma cells for which responses by autologous T cells have been detected. To evaluate the frequency with which **tyrosinase**-specific T cells can be isolated from melanoma patients for potential use in therapy, a recombinant vaccinia virus expressing **tyrosinase** was constructed for infection of autologous APCs that could be used to stimulate T cells reactive with this protein. Eight patients were studied, with peripheral blood serving as the source of both responder T cells and autologous APCs. **Tyrosinase**-specific CD8+ CTL clones were isolated from five of the eight patients with melanoma. The **tyrosinase**-specific CTL generated in this manner recognized autologous tumor cells as well as targets expressing the recombinant virus vector. CTL clones from three of the individuals were restricted to HLA-A28, -B8, and -B60, which have not previously been identified as alleles that can present immunogenic **tyrosinase** peptides. **Tyrosinase**-specific **CD4**+ T cell clones were isolated from six of the eight patients by stimulation with autologous APCs infected with recombinant vaccinia virus, and all these **CD4**+ clones were capable of recognizing autologous tumor cells. These studies demonstrate a high prevalence of **CD4**+ and CD8+ **tyrosinase**-specific responses in peripheral blood and support the feasibility of using peripheral blood to generate T cells for tumor therapy without the requirement for isolating T cells that have infilt

TI MHC class I-restricted recognition of a melanoma antigen by a human CD4+ tumor infiltrating lymphocyte.

AU Nishimura M I; Avichezer D; Custer M C; Lee C S; Chen C; Parkhurst M R; Diamond R A; Robbins P F; Schwartzentruber D J; Rosenberg S A

CS Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892, USA..

nishimur@helix.nih.gov

SO CANCER RESEARCH, (1999 Dec 15) 59 (24) 6230-8.

Journal code: CNF. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 200003

EW 20000305

AB It is generally considered that MHC class I-restricted antigens are recognized by CD8+ T cells, whereas **MHC** class **II** -restricted antigens are recognized by CD4+ T cells. In the present study, we report an MHC class I-restricted CD4+ T cell isolated from the tumor infiltrating lymphocytes (**TILs**) of a patient with metastatic melanoma. **TIL** 1383 I recognized HLA-A2+ melanoma cell lines but not autologous transformed B cells or fibroblasts. The antigen recognized by **TIL** 1383 I was **tyrosinase**, and the epitope was the 368-376 peptide. Antibody blocking assays confirmed that **TIL** 1383 I was MHC class I restricted, and the CD4 and CD8 coreceptors did not contribute significantly to antigen recognition. **TIL** 1383 I was weakly cytolytic and secreted cytokines in a pattern consistent with it being a Th1 cell. The avidity of **TIL** 1383 I for peptide pulsed targets is 10-100-fold lower than most melanoma-reactive CD8+ T cell clones. These CD4+ T cells may represent a relatively rare population of T cells that express a T-cell receptor capable of cross-reacting with an MHC class I/peptide complex with sufficient affinity to allow triggering in the ab